

In support of their application, Applicants also enclose with this response copies of the Declarations of Dr. Joseph Robert Emmott Fraser, M.D. and Dr. Eva Turley filed with Parent Application Serial No. 07/675,908 and a second Declaration of Dr. Eva Turley filed in respect of Application Serial No. 08/352,697.

These individuals previously filed Declarations in this case and the new Declarations contain additional evidence to assist the Examiner's examination of Applicants' application and advance such examination. The Declarations each contain six (6) representative claims of Parent Application Serial No. 07/675,908, (from which this divisional application was filed) as Exhibits to his/her Declaration (Exhibit 2 to Dr. Fraser's Declaration and Exhibit 1 to Dr. Turley's Declaration) which have been added to the claims in the parent application. These representative claims of the parent application (07/675,908), in Applicants' respectful submission, now address all of the Examiner's concerns under 35 U.S.C. §103 and, address the State of the Art (particularly United States Patent No. 4,736,024) which is verified by Dr. Fraser and Dr. Turley in their declarations enclosed and was discussed by the Experts (Dr. Laurent, Fraser, Turley, Moore, Roth et al) in the Declarations filed with the last response.

REJECTION OF CLAIMS UNDER 35 U.S.C. §103(a) AS BEING UNPATENTABLE
OVER DELLA VALLE (U.S. 4,736,024) IN COMBINATION WITH DELLA VALLE
(U.S. 5,336,767) AND LOWRY (U.S. 4,900,550)

The primary reference relied on by the Examiner, in rejecting Applicants' claimed invention under 35 U.S.C. §103, is United States Patent 4,736,024 (Fidia), filed April 3, 1986 (claiming priority from Italian Application filed 1985) and issued April 5, 1988, which purports to teach pharmaceutical preparations for topical use particularly ophthalmic use comprising an active pharmacological substance or a mixture of pharmacologically substances, either active or suitable

for topical administration and a vehicle which purports to comprise hyaluronic acid or a molecular fraction of hyaluronic acid or a salt of same either alone or with an alkaline metal, or pharmacologically substances, optionally together with additional conventional excipients. The two molecular fractions involve hyalectin and hyalastin (so called by Fidia) which have the following characteristics purportedly found by Della Valle (Fidia).

Applicants have carefully reviewed Della Valle (U.S. Patent 4,736,024) and particularly the statements at column 9 which discuss that the concentrations of the solutions taught therein which may vary within wide limits, for example between 0.01% and 75%, by both of each of the two components taken separately and their mixtures or salts (note both cannot, in reality, be 75% of the composition.) Thus, the concentrations of the components are from very small concentrations to very large concentrations and any mixture therebetween. The concentrations in order of magnitude can vary more than 7,500 fold. According to Dr. Turley (in the Declaration filed with respect to Application Serial No. 08/352,697) and a copy of same enclosed herewith), the concentrations at column 9 are so broad as to be meaningless and unrealistic (see paragraphs 11 and 12 of the Declaration). No person skilled in the art would know what compositions are suitable for what dosages or conditions. "Undue experimentation" would be required to determine what concentrations of hyaluronan and medicine can make up compositions for treating unknown diseases and conditions (which must be determined). In other words, Della Valle would have to invent Applicants' invention. Applicants' combination of the form of hyaluronic acid (having a minimum amount of 10mg) together with an agent (for example, antibiotics, antibacterials, antimicrobial and anti-metabolite) which is suitable for treating diseases and conditions involving underperfused tissue and pathological tissue in humans as provided in the claims are not taught either explicitly or implicitly in Della Valle anywhere.

Further, the law is such that a selection within these "meaningless and unrealistic" concentrations which selection provides unexpected results can itself be patented as they have not been taught previously. The treatment with these compositions providing unexpected results can also be patented. Provided there are unexpected results, this uniqueness may even be further enhanced by the specific choice of drugs, for example where the drug is anti-metabolite. In other words, where the prior art is a "paper" document and does not teach Applicants' compositions, these compositions can be patented by Applicants if they provide unexpected utility (which they do). Additionally, the dosages taken from the composition and methods of treatment which are both new and which treatments use dosages taken from the composition are also patentable.

As noted by both Drs. Fraser and Turley, where the treatment involves underperfused tissue and/or pathological tissue the form of hyaluronan, according to the teachings of Applicants' application when included in the dosages targets the underperfused tissue and/or pathological tissue and transports (delivers) the agent (medicinal agent and therapeutic agent) which is to be used to treat the underperfused tissue and/or pathological tissue, to the tissue. The agent is an agent that is suitable for use to treat the underperfused and/or pathological tissue, and the form of hyaluronic acid transports the agent to the site (pathological tissue and/or underperfused tissue). A detailed discussion of this transport of the agent to the site by the form of hyaluronic acid and the agents being transported (delivered) to the pathological tissue and/or underperfused tissue is provided, throughout the application. Applicants direct the Examiner's attention to page 23, line 30 to page 36, line 1.

Applicants respectively submit that the amended method and dosage claims provide successful treatment of the disease and the conditions (for

example, infection) involving underperfused tissue and pathological tissue in human selected from the group by employing an effective amount of a medicinal agent, for example an antibiotic agent and a sufficient amount of a form of hyaluronic acid sufficient to facilitate the agents penetrations and transportation to the site in need of treatment. The minimum dosage amount and the specific molecular weight of hyaluronic acid disclosed and claimed in applicant's application enhances the performance of the drug in the human body and produces the unusual targeting of the conditions and the diseases involving underperfused tissue and the pathological tissue, as would be understood by persons skilled in the art (as discussed by Dr. Fraser and Dr. Turley). Applicants submit the teaching of applicant's application and the claims are not suggested by Della Valle or any other prior art (see pages 18 to 20 of Dr. Fraser's declaration).

WHAT DOES DELLA VALLE TEACH?

The Examiner states (starting at page 2, paragraph 6 to page 3, paragraph 1 of the Official Action) that Applicants' combination is disclosed by Della Valle et al. The Examiner also suggests that the dosage amount of the hyaluronic acid and drug which is within the claimed amount is disclosed at column 9 of Della Valle. The Examiner further states that the teaching by Della Valle et al is not limited to the use in ophthalmology and also covers a broad range of concentrations and dosages.

Applicants respectfully disagree with the conclusions of the Examiner because persons skilled in the art would not use the teachings of Della Valle (or any of the prior art) to prepare dermatological preparations using hyaluronic acid (without other ingredients that were expected to penetrate or to keep the mixture wet). because the hyaluronic acid was expected by such persons to dry up and flake off or on mucous membranes, be diluted and washed away by, for example, saliva (in this regard the Examiner is respectfully requested to review the

enclosed Declaration of Dr. Fraser which was filed with respect to Parent Application Serial No. 07/675,908, particularly paragraphs (c) through (e) on pages 10-12 of the Declaration). That was the whole point of submitting the prior art with the previous response in the prosecution of this application.

After referring to Dr. Laurent's statement (page 3, paragraph 2 of the Official Action) dealing with the hyaluronic acid as potentiating the action of the drug, the Examiner has stated that the "Declarations fail to present any data showing that hyaluronic acid enhances the ability of known medicines." Applicants respectfully traverse the conclusion of the Examiner because the application as filed fully discloses and teaches persons skilled in the art that a minimum amount of 10mg of hyaluronic acid enhances the transportation and delivery of the medicine (for example, antibiotics) to a site in need of treatment. In this regard, the Examiner is respectfully requested to review Applicants' application at page 24, beginning at line 13 wherein the use of a sufficient amount of hyaluronic acid (a minimum amount of 10mg when administered together with the drugs, for example, ascorbic acid) produces an unusual targeting for the underperfused tissue or pathological tissue. Starting at line 23 on page 24 of the application, Applicants teach that:

"The hyaluronic acid enhances the anti-neoplastic activity and effect of the ascorbic acid. It is thought that this enhanced activity eliminates the free radicals by acting as a free radical scavenger. In any event the patients feel better. This is also demonstrated with furosemide and hyaluronic acid where the activity of furosemide is enhanced only minimally when administered with hyaluronic acid to a "normal" subject but the activity is enhanced significantly when administered to a patient whose kidney is underperfused or malfunctioning due to insufficient intra-vascular volume."

At page 67, lines 18 to 28, further test results are provided as follows:

"Enhanced Activity of Antibiotics with hyaluronic acid. A chronic abscess rat model was used. Sprague Dawley Rats were used. Pellets

of bacteria were inserted into each of the bellies of the rats and then the rats were treated as indicated. In this model therapeutic activity of gentamycin was compared to gentamycin in hyaluronic acid the results demonstrate a statistically significant improvement by the combination over the antibiotic alone. In this regard lower doses of antibiotic in antibiotic refractory situations were required as a result of the antibiotic being administered with hyaluronic acid. Please refer to Figure 1/1 of the drawings."

A detailed discussion of enhancement (potentiation) and transport of the agent to the site in need of treatment by the form of hyaluronic acid is provided throughout the application. Applicants direct the Examiner's attention to page 23, lines 3 to page 36, line 1. Note the statement between the bottom of page 33, line 37 to the top of page 34, line 2, when the form of hyaluronic acid is combined with the therapeutic agent for treatment of the diseases and conditions the results are totally unexpected (see also the additional test result at page 68 where the use of hyaluronic acid enhanced the ability of known medicine).

In Applicants' respectful submission, it is to this enhancing ability of hyaluronic acid that the statement of Dr. Laurent is referring to. Dr. Laurent, by this statement, is confirming the examples and teachings found in Applicants' application as filed. Applicant's disclosure of their invention is addressed to persons skilled in the art. In light of the above submissions and experts' declarations, the Examiner has the burden of showing that the disclosure does not teach how the invention is to be used. Applicant's respectively submit this burden has not been overcome by the Examiner. In this regard, the application is very clear. Applicant's have discharged any burden upon them when filing the original application by disclosing their claimed invention in a clear and unambiguous manner such that persons skilled in the art understand and can use the invention. The Examiner is respectfully reminded that examination before the United States Patent and Trademark Office is not examination before

the Food and Drug Administration (FDA) and Applicants are not seeking FDA approval from the Examiner.

With respect to the prior art teaching, applicants submit that Della Valle made beakers of material (see, for example, the formulations discussed at column 9, line 36 to column 10, line 17); however, the dosages applied in the entire reference are drops. Nowhere is there a teaching of the use of anything but drops. These drops are administered to the eye. The Examiner will note that the use of hyaluronan in the eye in small drops has been tested by Dr. Ian Constable and the result published in Round Table Series #40, 1995 (see article entitled "Subretinal neovascularization and possible hyaluronan-targeted therapy"). In this article, a copy of which is attached as Exhibit 3 to the Declaration of Drs. Fraser and Turley, Professor Constable discusses the administration of drops of hyaluronan and non-steroidal anti-inflammatory drugs in the eye. He clearly states at page 141:

"It does not get to the back of the eye. Available data on combining HA with drugs in drops show rapid clearance from the anterior chamber. Dr. Gustafson has published data on receptors in the corneal epithelium, and nothing gets to the back of the eye if administered as drops."

These tests clearly show that the use of hyaluronan in the eye in small drops (as described in Della Valle) cannot penetrate the skin or even adhere to as they did in the eye. The eye is not the skin or mucous membranes. Della Valle, in addition to stating what is stated at column 9, lines 3 to 6 suggests that the dosages having these concentrations can be used dermatologically (see column 2, lines 54 to 59). However, from the declaration of Dr. Turley, the Examiner will note that no persons skilled in the art would understand Della Valle to teach

compositions to be used on the skin or on mucous membrane tissue for the purposes of applying a medicine. The reason is that persons skilled in the art, both before and after the filing of the Della Valle patent application filed April 3, 1986 which issued as United States Patent 4,736,024 would have believed (a) if applied topically compositions containing hyaluronan and a medicine would have dried on the skin and flaked off, and (b) if applied to the mucous membranes, the compositions would have been diluted and washed away.

Thus, no person skilled in the art would use the teachings of Della Valle to make any dermatological preparation.

To this day there is no evidence that Della Valle has marketed anything in accordance with these teachings. No person skilled in the art would use Della Valle to produce any composition for dermatological use let alone Applicants' compositions. Thus, Applicants' claims for the dosage amount of a pharmaceutical composition having the specified amount is clearly not taught or contemplated by Della Valle. In this regard, Applicants have discovered compositions which have the minimum amount of 10mg of the form of hyaluronan and active which provide the unique ability to treat all the diseases and conditions indicated in the patent application. Della Valle did not know of transportation. Della Valle, in effect, stated that medicines could be mixed with hyaluronic acid. However, the amounts of hyaluronic acid which provide the transportation are not contemplated by Della Valle. These dosage amounts with the specific molecular weight were not contemplated in Della Valle or anywhere in the prior art. This unique combination of hyaluronic acid with the medicine gave the unique combination by providing the appropriate dosage amount of hyaluronic acid to achieve the unique successful treatments.

Furthermore, Applicants have now shown by expert testimony that Della Valle (4,736,024) is irrelevant. Della Valle et al (5,336,767), the Examiner purports to teach the administration of esters of hyaluronic acid with drugs including antibiotics, antibacterials and antiviral agents. Although the enclosed declarations are directed to Della Valle (4,736,024), after careful review of Della Valle (5,336,767), the comments found in the declarations in Applicants' opinion, are applicable to the teachings of Della Valle (5,336,767). Della Valle (5,336,767) does not teach, infer, nor imply a method of treating a condition or disease involving underperfused tissue or pathological tissue in a human comprising administering an effective dosage amount of a medicinal or a therapeutic agent for treating the condition or disease wherein the medicinal agent is facilitated for penetration of the agent through the tissue by a sufficient dosage amount of a form of hyaluronic acid at a site to be treated. There is no teaching whatsoever of the use of a form of hyaluronic acid which (a) facilitates transportation and penetration, (b) has a molecular weight in the range of 150,000 to 750,000 daltons, and (c) provides a dosage greater than 10mg. Applicants respectfully submit there is clearly no motivation to arrive at Applicant's invention. Thus Applicants' invention is neither taught nor inferred in Della Valle (5,336,767), alone or combined with any other reference of record. Therefore, reconsideration of the claims is respectfully requested.

Furthermore, the Examiner relies on Lowry stating that the reference discloses a composition containing hyaluronic acid which is effective as a cell penetrant. Applicants respectfully traverse the conclusion of the Examiner with respect to the teachings of Lowry (United States Patent No. 4,900,550). Lowry purports to disclose a cosmetic formulation for use with a skin care cosmetic regime for accelerating the cell renewal cycle of the skin to provide younger looking skin. The cosmetic formulation (the one preparation) listed in columns

3 and 4 of Lowry's patent is formulated of the specific ingredients to achieve the conditioning of a person's skin.

The Examiner will note that propylene glycol is a penetrant (penetrating agent), present in an amount of 3%. The presence of propylene glycol in the cosmetic formulation of Lowry's patent (U.S. Patent 4,900,550) is to increase the penetration and therapeutic activity (cell renewal cycle of the skin) of the formulation. Thus, increased penetration of the cell is achieved due to the presence of propylene glycol in the formulation. The effect of propylene glycol on skin penetration is well known in the art (both prior to and after the filing of Lowry's patent). In this regard, Applicants enclose United States Patent No. 4,808,576 (attached as **Schedule "A"**) which teaches the use of propylene glycol as a transdermal carrier (see column 6, lines 1-9) and abstracts of two articles published in International Journal of Pharmacy, 1986, 28:201-209 (attached as **Schedule "B"**) and Journal of Pharmaceutical Science, 1993, 82(5):551-552 (attached as **Schedule "C"**) wherein the use of propylene glycol as a penetrating agent is discussed.

There is no teaching in the patent (U.S. Patent 4,900,550) that hyaluronic acid, especially about .1%, does anything (.1% would not give minimum of 10mg when the composition of Lowry is applied). Applicants submit that Lowry does not disclose a dosage amount of a pharmaceutical composition or a method of treating diseases and conditions involving underperfused tissue and pathological tissue in a human comprising administering an effective amount of an agent (for example, an antibiotic agent) wherein the agent is facilitated for penetration by a sufficient amount of a form of hyaluronic acid having a molecular weight greater than 150,000 daltons and less than 750,000 daltons to a site in need of treatment. Furthermore, Lowry does not teach the use of a minimum amount of hyaluronic acid which is taught in Applicants' application. The Examiner will agree that

Applicants' invention is based on the treatment of disease and conditions involving underperfused tissue and/or pathological tissue by the effective dosage amount of an agent (for example, anti-microbials), wherein the form of hyaluronic acid (having a minimum amount of 10mg) enhances the activity and effect of the agent.

In summary, Lowry does not teach the use of a form of hyaluronic acid to deliver medicines or therapeutic agents or any agents. There is nothing in Lowry to teach the delivery of anything by hyaluronic acid. Applicants submit that persons skilled in the art would give Lowry minimal effect, if any, and would definitely not think of Lowry in respect of the transport or deliver of medicines or agents. There is no motivation to combine Lowry and Della Valle because there is no recognition of transport by the form of hyaluronic acid. There is no leading, by either or both of the references, to the unexpected utility of Applicants' invention - unexpected unobvious results provided by Applicants' dosage and method of treatment with those dosage namely, targeting, delivery, and transport.

Applicants submit that there is no evidence whatsoever in Della Valle (or Lowry) that Della Valle (or Lowry) delivers any material into the skin. Della Valle only provides a statement of dermatological application but the dermatological application would not be used by persons skilled in the art because they expect that the composition cannot get in. Persons skilled in the art therefore would not make the compositions, and particularly would not make the compositions in the minimum dosage amount given and with the drugs given in the claims. These compositions and methods give unexpected utility and thus are patentable.

It is clear from the law and to reiterate as previously stated, obviousness is a question of fact. The compositions with the limitations in the claims as amended are not old; the methods taught in this application are completely new - not old and the dosages claimed in Claim 122, 151 and 261 are not old.

STATE OF THE ART

OVERVIEW

With respect to the State of the Art with respect to hyaluronan, Dr. Fraser and Dr. Turley have set out the state of the art to enable the Examiner to better understand Della Valle and the implications of this purported teaching. It should now be clear that persons skilled in the art would not make dermatological compositions or other compositions having regard to Della Valle's teachings because the dosage amounts would, when applied topically, **be expected to dry up and flake off** before any medicine would be expected to be absorbed by the skin. With respect to applications to mucous membranes, the dosage amounts would be washed away and diluted and would not be expected to provide any benefits. This is discussed in paragraph 4 of Dr. Fraser's Declaration and paragraph 4 of Dr. Turley's declaration.

Applicants set out below the historical state of the prior art (discussed in the Expert Declarations) with respect to Della Valle so that the Examiner has the chronological teachings to show that not only before the filing of Della Valle, but after the filing, persons skilled in the art did not believe that hyaluronic acid got into the skin.

"DETAILED DISCUSSION OF PRIOR ART"

(a) U.S. Patent 3,887,703 (issued June 3, 1975) teaches in examples 13, 14, 15 and 17 combinations of mucopolysaccharides (which include hyaluronan), together with medicines. Drops of this solution were applied onto the hair and scalp. The

drops would each contain much less than 1mg of the form of hyaluronic acid. Persons skilled in the art expected that whatever was applied would sit there, dry up and flake off (see Dr. Turley's Declaration).

(b) U.S. Patent 4,141,973, which issued February 27, 1979 teaches high molecular weight forms of hyaluronic acid. At column 14, Balazs indicates that the high molecular weight form of hyaluronan can be used as a vehicle for any kind of intra-articular medication to protect the articular cartilage from the possible harmful effects of the particular drug used and to prolong the effect of the drug by decreasing its diffusion out of the articular space. Balazs, a world leader, did not specify any use to the skin as a carrier for drugs. To persons skilled in the art this teaching means that the combination of the form of hyaluronan having the high molecular weight, together with the, for example, corticosteroid is injected into the intra-articular space and because of the high molecular weight of the hyaluronic acid the effect of the drug is prolonged by decreasing (delaying) its diffusion out of the articular space providing a retard effect. The high molecular weight hyaluronan remains in the intraarticular cavity and the medicine (for example, corticosteroid) leaches therefrom and is absorbed.

(c) United States Patent 4,711,780, which issued December 8, 1987, teaches a composition for treating the surface epithelium and a process for promoting epithelial regeneration. At column 5, example 2, the patentee indicates that mucopolysaccharide (which include hyaluronan) acts as a barrier:

"In order to document that mucopolysaccharide acts as a barrier, thereby preventing toxins on the skin surface from penetrating into the blood circulation system which otherwise leads to septicemia..."

The hyaluronan is high molecular weight.

(d) In the article found in "Polymers", in Cosmetics and Toiletries, Vol. 99, June 1984, entitled "Hyaluronic Acid, Its Structure and Use", at page 71 Balazs et al (the same Balazs in U.S. Patent 4,141,973) state:

"The stratum corneum is known to be impermeable to molecules as large as hyaluronic acid."

"Therefore, it is not expected that even very short chains of oligosaccharides of degraded hyaluronic acid that contain more than 5 to 10 pentisaccharide units can pass through this layer of the skin. There is no evidence in the literature that any hyaluronic acid - in any solvent or with any added carrier - will penetrate deeper than the crevices between the desquamating cells."

These statements were made in 1984.

(e) Finally, in an article entitled "Effect of Several Penetration Enhancers on the Percutaneous Absorption of Indomethacin in Hairless Rats", Chem. Pharm. Bull. 36(4), 1519-1528 (1988) there is a discussion of the effect of several penetration enhancers on the percutaneous absorption of drugs. Note the use of the expression "percutaneous absorption". In other words the medicine is absorbed through the skin and the penetration enhancers enable such absorption. One of the compounds tested is sodium hyaluronate and the clinicians found that it had no enhancing effect on the skin permeation of indomethacin.

MOSAICING OF PRIOR ART

Further, with respect to the alleged obviousness of Applicants' invention by the combination of teachings from the references asserted by the Examiner, factually Della Valle or Lowry do not relate to the use of a minimum amount of forms of hyaluronic acid to deliver medicines or therapeutic agents or any agent. Della Valle is discussed above and the discussion is emphasized herein again. Other prior art is further discussed by both Dr. Fraser and Dr. Turley. Couple their statements with those of their previous declarations and it is clear Della Valle is not relevant.

Applicants repeat their assertions about the law previously made. However, Applicants will refer to only one recent decision, that of United States Court of Appeals dealing with "Obviousness" under 35 U.S.C. §103 in In re Michihiko Ochiai, et al., 37 U.S.P.Q. 2d, 1127. In that case, the United States Court of Appeals stated as follows:

The test of obviousness *vel non* is statutory. It requires that one compare the claim's 'subject matter as a whole' with the prior art 'to which said subject matter pertains.' 35 U.S.C. § 103. **The inquiry is thus highly fact-specific by design.** This is so 'whether the invention be a process for making or a process of using, or some other process.' *Kuehl*, 475 F.2d at 665, 177 USPQ at 255. **When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned.** *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

(emphasis added by Applicants' Agent)

It is therefore clear;

- (a) The subject matter of Applicants' claims as presented is taught by their application;
- (b) the subject matter of the claims is not obvious over the prior art;
- (c) Applicants' treatments provide unexpected utility - in this regard see all the results of all the tests submitted in both the application and the additional test results filed in Declarations filed with previous responses (Declarations of Professor Torvard Laurent, Dr. Robert Fraser, Professor Ian Constable, Dr. Eva Turley, Dr. Stefan Gustafson, Dr. Adrian Moore, Dr. Sanford Roth, Dr. George DeVeber and Stellan Lind). Particularly, the Examiner is reminded of the statements at page 23, line 36 to page 24, line 6 of the application as follows:

"By way of example and to illustrate the facilitation of the delivery or transport of a chemical to a site in a mammal, when ethyl alcohol is injected directly into a tumor, and sonographic (ultrasound) assessment is made, it is not dispersed throughout the tumor. When the ethyl alcohol to be administered into a tumor is carried by hyaluronic acid and/or salts thereof, sonographic assessment of the tumor, demonstrates the dispersion of the ethyl alcohol throughout the tumor."

There is no evidence to contradict this evidence.

Throughout the application, evidence is provided that the treatments are unexpected. There is no evidence to contradict (see Case XII, particularly lines 17-21, for example). The dosages used are not known and not obvious.

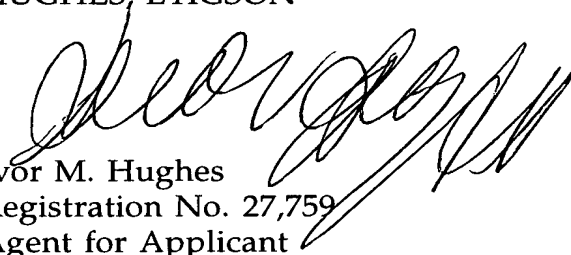
Applicants therefore respectfully submit that the application is in condition for allowance and same is solicited at the earliest convenience. When the Examiner has reached this file for examination and has had a chance to

review the material she is kindly requested to contact Applicants' agent to discuss arranging a meeting where the claims and the nature of the claims can be discussed.

If the Examiner, in the interim, has any questions, she is respectfully requested to contact Applicants' Agent, Ivor Hughes at (905) 771-6414 collect at her convenience.

Respectfully submitted,

HUGHES, ETIGSON


Ivor M. Hughes
Registration No. 27,759
Agent for Applicant

STT*kdk

Enclosures:

1. ✓ Request for 2-Month Extension of Time
2. ✓ Petition pursuant to §1.129(a) to Withdraw Final Rejection
3. ✓ Cheques for \$390.00 U.S. and \$770.00 U.S.
4. ✓ Substitute Specification
5. ✓ Declaration of Dr. Eva Turley filed in Application Serial No. 08/352,697
6. ✓ Declarations of Drs. Turley and Fraser filed in 07/675,908
7. ✓ United States Patent No. 4,808,576 (attached as **Schedule "A"**)
8. ✓ Abstract of article published in International Journal of Pharmacy, 1986, 28:201-209 (attached as **Schedule "B"**)
9. ✓ Abstract of article published in Journal of Pharmaceutical Science, 1993, 82(5):551-552 (attached as **Schedule "C"**)
10. ✓ Substitute Specification



08/11/97

SEP 5

IN THE UNITED STATES PATENT OFFICE

In re application of:

Rudolf E. Falk and Samuel S. Asculai

Serial No.: 08/462,147

Group Art Unit : 1211

Filed : June 5, 1995

Examiner : Elli Peseelev

For : TREATMENT OF CONDITIONS AND DISEASE

#10

**APPLICATION TO HAVE THE PATENT OFFICE
WITHDRAW THE FINAL REJECTION
UNDER TRANSITIONAL PROVISION 37 C.F.R. §1.129**

The Honorable Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia 22202
U.S.A.

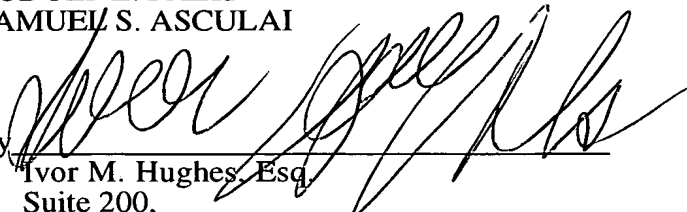
Dear Sir:

Applicants hereby request that the Final Rejection issued in the prosecution of this Application be withdrawn under the Transitional Provision under 37 C.F.R. §1.129(a) because this Application has been pending within the meaning of Transitional Provision 37 C.F.R. §1.129(a) for more than two years before June 8, 1995. This application was filed June 5, 1995, which is a divisional application of United States Patent Application Serial No. 07/675,908, first filed under PCT Application Serial No. PCT/CA90/00306, filed on the 18th day of September, 1990 (claiming priority from Canadian Patent Application Serial No. 612,307, filed on the 21st day of September, 1989) and entering the National Phase in the United States on the 3rd day of July, 1991, more than two years before June 8, 1995.

Applicants also enclose the fee of \$770.00 U.S. to cover the fee in Section §1.17(r). If there is any deficiency or surplusage of the fee enclosed, please obtain any such deficiency from or credit the surplusage to Deposit Account No. 08-3255 and advise Applicant's Agent.

Respectfully submitted,
RUDOLF E. FALK
SAMUEL S. ASCULAI

By


Ivor M. Hughes, Esq.
Suite 200,
175 Commerce Valley Drive West,
Thornhill, Ontario.
L3T 7P6 CANADA

09/02/1997 TWILLIAM 00000027 08462147
02 FC:146 770.00 OP

August 8, 1997
Our Ref. P-0800(O)-3

Agent for Applicant
(905) 771-6414

SCHEDULE "A1"

**Transitional Procedures for limited
examination after final rejection
and restriction practice**

37 C.F.R. § 1.129(a)

TRANSITIONAL PROVISIONS

§ 1.129 Transitional procedures for limited examination after final rejection and restriction practice.

(a) An applicant in an application, other than for reissue or a design patent, that has been pending for at least two years as of June 8, 1995, taking into account any reference made in such application to any earlier filed application under 35 U.S.C. 120, 121 and 365(c), is entitled to have a first submission entered and considered on the merits after final rejection under the following circumstances: The Office will consider such a submission, if the first submission and the fee set forth in § 1.17(r) are filed prior to the filing of an appeal brief and prior to abandonment of the application. The finality of the final rejection is automatically withdrawn upon the timely filing of the submission and payment of the fee set forth in § 1.17(r). If a subsequent final rejection is made in the application, applicant is entitled to have a second submission entered and considered on the merits after the subsequent final rejection under the following circumstances: The Office will consider such a submission, if the second submission and a second fee set forth in § 1.17(r) are filed prior to the filing of an appeal brief and prior to abandonment of the application. The finality of the subsequent final rejection is automatically withdrawn upon the timely filing of the submission and payment of the second fee set forth in § 1.17(r). Any submission filed after a final rejection made in an application subsequent to the fee set forth in § 1.17(r) having been twice paid will be treated as set forth in § 1.116. A submission as used in this paragraph includes, but is not limited to, an information disclosure statement, an amendment to the written description, claims or drawings and a new substantive argument or new evidence in support of patentability.

(b)(1) In an application, other than for reissue or a design patent, that has been pending for at least three years as of June 8, 1995, taking into account any reference made in the application to any earlier filed application under 35 U.S.C. 120, 121 and 365(c), no requirement for restriction or for the filing of divisional applications shall be made or maintained in the application after June 8, 1995, except where:

(i) The requirement was first made in the application or any earlier filed application under 35 U.S.C. 120, 121 and 365(c) more than two months prior to April 8, 1995;

(ii) The examiner has not made a requirement for restriction in the present or parent application prior to April 8, 1995, due to actions by the applicant; or

(iii) The required fee for examination of each additional invention was not paid.

(2) If the application contains more than one independent and distinct invention and a requirement for restriction or for the filing of divisional applications cannot be made or maintained pursuant to this paragraph, applicant will be so notified and given a time period to:

(i) Elect the invention or inventions to be searched and examined, if no election has been made prior to the notice, and pay the fee set forth in § 1.17(s) for each independent and distinct invention claimed in the application in excess of one which applicant elects;

(ii) Confirm an election made prior to the notice and pay the fee set forth in § 1.17(s) for each independent and distinct invention claimed in the application in addition to the one invention which applicant previously elected; or

(iii) File a petition under this section traversing the requirement. If the required petition is filed in a timely manner, the original time period for electing and paying

U. S. PATENT AND TRADEMARK OFFICE

Effective October 1, 1996

The U. S. Patent and Trademark Office has amended its rules of practice in patent cases, Part I of Title 37, Code of Federal Regulations to adjust certain patent fee amounts to reflect fluctuations in the Consumer Price Index (CPI).

Any fee payment due and paid on or after October 1, 1996, must be paid in the revised amount. The date of mailing indicated on a proper Certificate of Mailing or Transmission under 37 CFR 1.8 will be considered to be the date of receipt and payment in the Office.

As this fee sheet is a summary and the content of rules also may be changing, you should refer to the notice published in the *Federal Register* on July 30, 1996 in Volume 61, Number 147, pages 39585 through 39592. See also the *Official Gazette of the United States Patent and Trademark Office* of August 20, 1996. The fees which are subject to reduction for small entities who have established status (37 CFR 1.27) are shown in a separate column.

For additional information, please contact the PTO General Information Services Division at (800) PTO-9199 or (703) 308-4357.

Fee Code	37 CFR	Description	Fee	Small Entity Fee if applicable
Patent Filing Fees				
101 / 201	1.16(a)	Basic filing fee - utility	770.00	385.00
102 / 202	1.16(b)	Independent claims in excess of three	80.00	40.00
103 / 203	1.16(c)	Claims in excess of twenty	22.00	11.00
104 / 204	1.16(d)	Multiple dependent claim	260.00	130.00
105 / 205	1.16(e)	Surcharge - Late filing fee or oath or declaration	130.00	65.00
106 / 206	1.16(f)	Design filing fee	320.00	160.00
107 / 207	1.16(g)	Plant filing fee	530.00	265.00
108 / 208	1.16(h)	Reissue filing fee	770.00	385.00
109 / 209	1.16(i)	Reissue independent claims over original patent	80.00	40.00
110 / 210	1.16(j)	Reissue claims in excess of 20 and over original patent	22.00	11.00
114 / 214	1.16(k)	Provisional application filing fee	150.00	75.00
127 / 227	1.16(l)	Surcharge - Late provisional filing fee or cover sheet	50.00	25.00
139	1.17(k)	Non-English specification	130.00	
Patent Issue Fees				
142 / 242	1.18(a)	Utility issue fee	1,290.00	645.00
143 / 243	1.18(b)	Design issue fee	440.00	220.00
144 / 244	1.18(c)	Plant issue fee	650.00	325.00
Patent Maintenance Fees Applications Filed on or after December 12, 1980				
183 / 283	1.20(e)	Due at 3.5 years	1,020.00	510.00
184 / 284	1.20(f)	Due at 7.5 years	2,050.00	1,025.00
185 / 285	1.20(g)	Due at 11.5 years	3,080.00	1,540.00
186 / 286	1.20(h)	Surcharge - Late payment within 6 months.	130.00	65.00
187	1.20(i)(1)	Surcharge after expiration - Late payment is unavoidable	680.00	
188	1.20(i)(2)	Surcharge after expiration - Late payment is unintentional	1,600.00	
Miscellaneous Patent Fees				
111	1.20(j)(1)	Extension of term of patent	1,090.00	
124	1.20(j)(2)	Initial application for interim extension (see 37 CFR 1.790)	410.00	
125	1.20(j)(3)	Subsequent application for interim extension (see 37 CFR 1.790)	210.00	
112	1.17(n)	Requesting publication of SIR - Prior to examiner's action	900.00*	
113	1.17(o)	Requesting publication of SIR - After examiner's action	1,790.00*	
146 / 246	1.17(r)	For filing a submission after final rejection (see 37 CFR 1.129(a))	770.00	385.00
149 / 249	1.17(s)	For each additional invention to be examined (see 37 CFR 1.129(b))	770.00	385.00
145	1.20(a)	Certificate of correction	100.00	
147	1.20(c)	For filing a request for reexamination	2,460.00	
148 / 248	1.20(d)	Statutory Disclaimer	110.00	55.00

*Reduced by Basic Filing Fee Paid

SCHEDULE "A2"

**Benefit of earlier filing date
in the United States**

37 C.F.R. § 120

such subsequent application has been withdrawn, abandoned, or otherwise disposed of, without having been laid open to public inspection and without leaving any rights outstanding, and has not served, nor thereafter shall serve, as a basis for claiming a right of priority.

Applications for inventors' certificates filed in a foreign country in which applicants have a right to apply, at their discretion, either for a patent or for an inventor's certificate shall be treated in this country in the same manner and have the same effect for purpose of the right of priority under this section as applications for patents, subject to the same conditions and requirements of this section as apply to applications for patents, provided such applicants are entitled to the benefits of the Stockholm Revision of the Paris Convention at the time of such filing.

(July 19, 1952, ch. 950, § 1, 66 Stat. 800; Oct. 3, 1961, Pub. L. 87-333, § 1, 75 Stat. 748; July 28, 1972, Pub. L. 92-358, § 1, 86 Stat. 502; Jan. 2, 1975, Pub. L. 93-596, § 1, 88 Stat. 1949.)

§ 120 Benefit of earlier filing date in the United States

An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

(July 19, 1952, ch. 950, § 1, 66 Stat. 800; Nov. 14, 1975, Pub. L. 94-131, § 9, 89 Stat. 691; Nov. 8, 1984, Pub. L. 98-622, § 104, 98 Stat. 3385.)

§ 121 Divisional applications

If two or more independent and distinct inventions are claimed in one application, the Commissioner may require the application to be restricted to one of the inventions. If the other invention is made the subject of a divisional application which complies with the requirements of section 120 of this title it shall be entitled to the benefit of the filing date of the original application. A patent issuing on an application with

SCHEDULE "B"

**Filing Receipt in respect of
Application Serial No. 08/462,147**

FILING RECEIPT



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTORNEY DOCKET NO.	DRWGS	TOT CL	IND CL
08/462,147	06/05/95	1205	\$1,034.00	P-0800(0)-3	1	10	7

IVOR M HUGHES
HUGHES ETIGSON
175 COMMERCE VALLEY
DRIVE WEST SUITE 200
THORNHILL ONTARIO CANADA L3T 7P6

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Application Processing Division's Customer Correction Branch within 10 days of receipt. Please provide a copy of the Filing Receipt with the changes noted thereon.

Applicant(s)

RUDOLF E. FALK, TORONTO, CANADA; SAMUEL S. ASCULAI,
TORONTO, CANADA.

CONTINUING DATA AS CLAIMED BY APPLICANT-

THIS APPLN IS A DIV OF 07/675,908 07/03/91

FOREIGN/PCT APPLICATIONS-CANADA

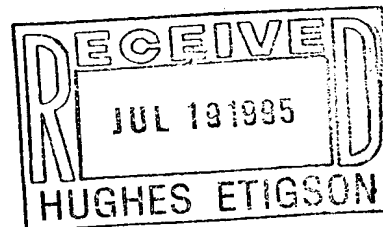
612,307

09/21/89

TITLE

TREATMENT OF CONDITIONS AND DISEASE

PRELIMINARY CLASS: 514



(see reverse)